## REMARKS

In the claim listing above, no claims have been amended, added or canceled. Accordingly, claims 251-287 and 625 continue to be presented for further examination in this application.

### Request For Continued Examination

Applicants are submitting herewith provided as Exhibit A their Request For Continued Examination (PTO/SB/30 (08-08). Authorization for the RCE fee required under 37 C.F.R. §1.17(e) is made in their RCE (Exhibit A).

Entry of Applicants' RCE is respectfully requested.

### Priority

The Examiner's comments regarding the priority date for this application are acknowledged. Applicants understand that the instant October 24, 2003 filing date has been used for prior art purposes.

### Withdrawal of Previous Rejections

Applicants appreciate the indication in the Office Communication (page 18, item 11) that in view of amendments in their last paper the previous objections to the specification and the claims have been withdrawn.

There are seven obviousness rejections that were made in the March 25, 2008 Office Communication.

### Commonality of Ownership

Applicants assert that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made.

**The First Rejection Under 35 USC §103**

Claims 251-264, 269-273, 275, 28 1-286, and 625 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Lin et al. (US 6,197,554 B1) in view of Laird et al. (EP 1 201768 A2). Comments directed to the first rejection are set forth on pages 3-8 in the Office Communication.

The first obviousness rejection is respectfully traversed.

At the outset, Applicants are incorporating by reference their remarks directed to the above rejection as set forth on pages 13-15 in their December 21, 2007 Amendment Under 37 C.F.R. §1.115. In the Office Communication (pages 19-20), however, additional comments were provided that were directed to Applicants' December 21, 2007 Amendment. Those additional comments from the Office Communication are provided below:

> Regarding the rejection of claims 251-264, 269-273, 275, 281-286, and 625 under 35 U.S.C. 103(a) as being unpatentable over Lin in view of Laird and the rejection of claim 625 under 35 U.S.C. 103(a) as being unpatentable over Borson in view of Laird, Applicant argues there is no motivation to combine the Laird reference with either of the Lin or Borson references for the following reasons: (1) The Lin reference is directed to library amplification, which comprises amplification of many target sequences, whereas the Laird reference is directed to the specific amplification of one or a small number of target sequences (pages 16-17 and 24), (2) The teachings of Laird are directed to minimizing primer-dimer formation, and therefore, are not applicable or relevant to the single-primer reverse transcription step taught by Lin (pages 17, 24, and 25), and (3) According to Laird, the incorporation of nucleotide analogs (2-0-methyl-nucleotides, 2'-amino-nucleotides, or 2'-fluoro-nucleotides) results in a delay in extension, which although useful for PCR methods where cycling between different temperatures is conducted, is not useful or likely to improve the reverse transcription step in the method of Lin, which is conducted at a single temperature (pages 17-18 and 25).
>
> Applicant's first argument was not found persuasive, because Laird does not limit the use of the modified primers to any particular type of amplification method, stating, "However, the invention is not restricted to any particular amplification system. The use of the modified primers in other primer-based amplification methods in which primer-dimer or non-specific amplification product can be formed is expected to be useful (paragraph 47 on page 7)." Based on these teachings of Laird, an ordinary artisan would have been motivated to use the modified primers of

Laird in any amplification reaction, such as the reverse transcription step performed in the method of Lin, in order to reduce template-dependent non-specific amplification.

Applicant's second argument was also unpersuasive, because Laird teaches using the modified primers to reduce template-dependent non-specific amplification in addition to template-independent non-specific amplification *(i.e.* primer-dimer formation) (see paragraph 47). In particular, Laird teaches that non-specific amplification can occur during the preparation of the amplification reaction mixture (see paragraphs 4 and 28), and that use of the modified primers can reduce this undesirable reaction (paragraphs 12-17, 28, and 47). Based on these teachings of Laird, an ordinary artisan would have been motivated to use the modified primers in the method of Lin in order to minimize the possibility of non-specific amplification occurring during the setup of the reverse transcription reactions.

Applicant's third argument was also unpersuasive, because Laird further teaches that the modified primers can be used in combination with other methods known in the art to be useful for reducing non-specific amplification. Thus, use of the modified primers in combination with other known methods of reducing non-specific amplification, as suggested by Laird (paragraph 53), would be expected to measurably reduce non-specific amplification in the method of Lin.

In response to the above additional comments in the Office Communication, Applicants offer the following remarks.

**(1) The Lin reference is directed to library amplification, which comprises amplification of many target sequences, whereas the Laird reference is directed to the specific amplification of one or a small number of target sequences (pages 16-17 and 24)**

Applicants' position regarding the linear library amplification method as disclosed in Lin et al. and specific exponential amplification as disclosed in Laird et al. still remains cogent and viable in the face of the instant rejection. The Office Communication misses this point which was offered initially in Applicants' December 21, 2007 Amendment. Regardless of how it is amplified – the target and its amplification are very different between Lin and Laird. In the case of Lin et al. and their library amplification method, there are a large number of different target sequences sought to be amplified. Lin's methods seek to generate linearly a complete full-length

cDNA library from single cells. In contrast to Lin et al., the primary reference, Laird's disclosure and examples are all directed to specific exponential amplification of a single or a few species. This is so even when in the Description of the Related Art Laird et al. cite different amplification technologies such as Mullis's PCR technology, Walker's system with SDA, Kwoh's transcription amplification system (TAS) and Guatelli's self-sustained sequence replication (3SR).

> The invention of the *polymerase chain reaction (PCR)* made possible the in vitro amplification of nucleic acid sequences. PCR is described in U.S. Pat. Nos. 4,683,195; 4,683,202; and 4,965,188; Saiki et al., 1985, Science 230:1350-1354; Mullis et al., 1986, Cold Springs Harbor Symp. Quant. Biol. 51:263-273; and Mullis and Faloona, 1987, Methods Enzymol. 155:335-350; each of which is incorporated herein by reference. The development and application of PCR are described extensively in the literature. For example, a range of PCR-related topics are discussed in PCR Technology--principles and applications for DNA amplification, 1989, (ed. H. A. Erlich) Stockton Press, New York; PCR Protocols: A guide to methods and applications, 1990, (ed. M. A. Innis et al.) Academic Press, San Diego; and PCR Strategies, 1995, (ed. M. A. Innis et al.) Academic Press, San Diego; each of which is incorporated herein by reference. Commercial vendors, such as Applied Biosystems (Foster City, Calif.), market PCR reagents and publish PCR protocols.
>
> Since the original publication of nucleic acid amplification, various primer-based nucleic acid amplification methods have been described including, but not limited to, the *strand displacement assay (Walker et al.*, 1992, Proc. Natl. Acad. Sci. USA 89:392-396, Walker et al. 1992, Nucleic Acids Res. 20:1691-1696, and U.S. Pat. No. 5,455,166) and the transcription-based amplification systems, including the methods described in U.S. Pat. Nos. 5,437,990; 5,409,818; and 5,399,491; the *transcription amplification system (TAS) (Kwoh et al.*, 1989, Proc. Natl. Acad. Sci. USA 86:1173-1177); and *self-sustained sequence replication (3SR) (Guatelli et al.*, 1990, Proc. Natl. Acad. Sci. USA 87:1874-1878 and WO 92/08800). All of the above references are incorporated herein by reference. A survey of amplification systems is provided in Abramson and Myers, 1993, Current Opinion in Biotechnology 4:41-47, incorporated herein by reference. [Col. 1, lines 19-54; emphasis added]

Laird et al. later refer to the same *specific* amplification systems:

> In a preferred embodiment, the modified primers o*f the present invention are used in the* polymerase chain reaction (PCR), described in U.S. Pat. Nos. 4,683,195; 4,683,202; and 4,965,188; Saiki et al., 1985,

> Science 230:1350-1354; Mullis et al., 1986, Cold Springs Harbor Symp. Quant. Biol. 51:263-273; and Mullis and Faloona, 1987, Methods Enzymol. 155:335-350; each of which is incorporated herein by reference. However, the invention is not restricted to any particular amplification system. The use of the modified primers in other primer-based amplification methods in which primer dimer or non-specific amplification product can be formed is expected to be useful. Examples of primer-based amplification methods include the *strand displacement assay (Walker et al.*, 1992, Proc. Natl. Acad. Sci. USA 89:392-396, Walker et al. 1992, Nucleic Acids Res. 20:1691-1696, and U.S. Pat. No. 5,455,166) and the *transcription-based amplification methods*, including the methods described in U.S. Pat. Nos. 5,437,990; 5,409,818; and 5,399,491; the transcription amplification system (TAS) (Kwoh et al., 1989, Proc. Natl. Acad. Sci. USA 86:1173-1177); and *self-sustained sequence replication (3SR) (Guatelli et al.*, 1990, Proc. Natl. Acad. Sci. USA 87:1874-1878 and WO 92/08800). All of the above references are incorporated herein by reference. A survey of amplification systems is provided in Abramson and Myers, 1993, Current Opinion in Biotechnology 4:41-47, incorporated herein by reference.

It is clear that Laird et al. are in fact limiting the use of modified primers to *specific* exponential amplification, and not to generalized linear amplification, such as library amplification where, for example, oligo T is used to make copies of any mRNAs having poly A sequences, and thus, oligo T is not used to make copies of any mRNAs lacking poly A sequences.

**(2) The teachings of Laird are directed to minimizing primer-dimer formation, and therefore, are not applicable or relevant to single-primer reverse transcription step taught by Lin (pages 17, 24, and 25)**

As set forth above, in Laird et al. and in all of the other amplification technologies referred to in Laird's disclosure, such amplification systems are *not* library amplification. The desired goal in Laird et al. is specific exponential amplification, and any non-specific binding, non-specific hybridization or non-specific amplification is *not* desired. In fact, there is no statement or disclosure in Laird et al. which speaks to the application of their disclosure to any amplification technology *except for* specific amplification which is exponential and classically suffers from non-specific amplification and primer-dimer formation. Linear amplification of a great many different target sequences, such as in

library amplification, is simply not contemplated by Laird et al. or a person of ordinary skill reading their disclosure.

The reason why Laird's teachings are not applicable or relevant to the single-primer reverse transcription step taught by Lin would apply to any linear system including the present invention. In Laird et al. and other exponential amplification systems, non-specific amplification and particularly primer-dimer formation are clearly cause for concern. In Lin et al., primer-dimer formation and other non-specific amplification is not a problem, unlike the case of Laird's specific exponential amplification.

**(3) According to Laird, the incorporation of nucleotide analogs (2'-O-methyl-nucleotides, 2'-amino-nucleotides, or 2'-fluoro-nucleotides) results in a delay in extension, which although useful for PCR methods where cycling between different temperatures is conducted, is not useful or likely to improve the reverse transcription step in the method of Lin, which is conducted at a single temperature (pages 17-18 and 25).**

As indicated above, in the case of library amplification, non-specific amplification and primer-dimer formation are not problematic events as in the case of Laird's specific exponential amplification methods. Thus, one of ordinary skill in the art would not have applied and combined Laird's disclosure with Lin et al., because the incentive for doing so, namely, reducing non-specific amplification and primer-dimer formation, does not exist for Lin et al. who never even mentions such events as being problematic.

In light of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the first obviousness rejection.

**The Second Rejection Under 35 USC §103**

Claims 265-268 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1201768) and in further in view of Willis et al. (US 6,858,412) and further in view of Moran et al. (Nucleic Acids Research (1996) 24(11): 2044-2052). The second rejection is provided on pages 9-10 in the Office Communication.

The second obviousness rejection is respectfully traversed.

In response, Applicants respectfully point out that Laird et al. is not properly combinable with Lin et al. One of ordinary skill in the art would not have applied Laird's disclosure to Lin et al. because the latter is not faced with the problem of non-specific amplification and primer-dimer formation. Because Lin and Laird are insufficient to reach the present invention, the addition of Willis and Moran does not cure the insufficiency of the former.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the second obviousness rejection.

**The Third Rejection Under 35 USC §103**

Claims 274 and 276 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Lin et al. (US 6,197,554 BI) in view of Laird et al. (EP 1201768) and further in view of Sousa et al. (US 5,849,546). The third rejection is provided on pages 11-12 in the Office Communication.

The third obviousness rejection is respectfully traversed.

In response, Applicants respectfully maintain that the problem of non-specific amplification and primer-dimers is not present in Lin et al. Further, Laird et al. is not properly combinable with Lin et al. because one of ordinary skill in the art would not have applied Laird's disclosure to the latter in which the problems being solved are not present. Because the primary and secondary references do not reach the present invention, the addition of Sousa also fails to render the present invention obvious.

In light of the foregoing, Applicants respectfully request reconsideration and withdrawal of the third obviousness rejection.

**The Fourth Rejection Under 35 USC §103**

Claims 277, 278, and 280 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Lin et al. (US 6,197,554 81) in view of Laird et al. (EP 1201768) and further in view of Steffens et al. (Genome Research (1995)5:393-399). The fourth

rejection is set forth on pages 12-14 in the Office Communication.

The fourth obviousness rejection is respectfully traversed.

In response, Applicants respectfully point out that one of ordinary skill in the art would not have applied Laird's disclosure to Lin et al. because the latter is not faced with the problem of non-specific amplification and primer-dimer formation. Because the primary and secondary references are deficient in their respective disclosures to reach the present invention, the addition of Steffens et al. must be similarly deficient.

Reconsideration and withdrawal of the fourth obviousness rejection is respectfully requested.

**The Fifth Rejection Under 35 USC §103**

Claim 279 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1201768) and further in view of Sousa et al. (US 5,849,546) and further in view of Steffens et al. (Genome Research (1995) 5: 393-399). The fifth rejection is set forth on pages 14-15 in the Office Communication.

The fifth obviousness rejection is respectfully traversed.

As in the case of the previous rejections, Applicants respectfully point out that for reasons given above, the primary and secondary references do not render the present invention obvious. Accordingly, the addition of Sousa et al. and Steffens et al. are likewise insufficient to render Applicants' invention obvious.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the fifth obviousness rejection.

**The Sixth Rejection Under 35 USC §103**

Claim 287 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et a]. (US 6,197,554 BI; cited previously) in view of Laird et al. (PP 1201768; newly cited) and further in view of Borson et al. (PCR Methods and Applications (1992)2: 144-148; newly cited). The sixth rejection is set forth on pages 15-16 in the Office

Communication.

The sixth obviousness rejection is respectfully traversed.

In response, Applicants respectfully point out the primary and secondary references are insufficient to render the present invention obvious for reasons given above. Thus, the addition of Borson et al. is similarly deficient and does not render the present invention and claim 287 obvious.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the sixth obviousness rejection.

**The Seventh Rejection Under 35 USC §103**

Claim 625 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Borson et al. (PCR Methods and Applications (1992) 2: 144-148) in view of Laird et al. (EP 1201768). The seventh rejection is set forth on pages 17-18 in the Office Communication.

The seventh obviousness rejection is respectfully

In response, Applicants respectfully point out that neither Borson nor Laird disclose a library amplification method, such as set forth in the present invention. Both Borson and Laird disclose specific exponential amplification which is altogether different from the instantly claimed library amplification.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the seventh obviousness rejection.

**Information Disclosure Statement**

Through their attorney, attorneys wish to bring several documents to the attention of the Examiner so that these documents can be made of record in this application and properly considered. Provided herewith in Exhibit B are eight (8) sheets of IDS forms including three (3) sheets of Form PTO/SB/08a (01-08) and five (5) sheets of Form PTO/SB/08b (01-08).

Applicants respectfully request that the documents listed in Exhibit B be made of record and considered by the Examiner.

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## SUMMARY AND CONCLUSIONS

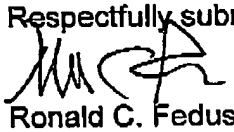
A complete listing of the claims in this application are provided above. No claims have been amended, added or canceled by this paper.

This paper is accompanied by Applicants' Request For Extension Of Time (3 Months), their Request For Continued Examination (Exhibit A) and their Information Disclosure Statement (Exhibit B). Authorization for the small entity fees for the accompanying papers have been made. No other fee or fees are believed due. In the event that any other fee or fees are due, however, authorization is hereby given to charge the amount of any such fee(s) to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Early and favorable action is respectfully requested.

Respectfully submitted,



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# EXHIBIT A